Moving Beyond Truvada for PrEP: The Next Generation of Biomedical HIV Prevention and What It Means for Los Angeles

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Presented at the Los Angeles County Commission on HIV
Thursday, July 14, 2016
RATIONALE

• Those who can readily access and adhere to multimodal HIV prevention strategies already do so

• For a significant minority, disorganizing effects of substance use, mental illness and other factors interfere with consistent engagement with ART as treatment or prevention

• This virtually assures a source for viremia, conferring status for this group as analogous to a “viral reservoir” at the population level

• Getting to zero infections will require more of those living with HIV to sustain viral suppression; those at high-risk to maintain consistent HIV prevention vigilance than is the current situation
MECHANISM OF LONG ACTING HIV PREVENTION

General Population

HIV Positive
At-Risk Negative

- Structural Factors
- Health Disparities
- Stigma
IN LOS ANGELES

- HPTN 061 showed a 6.9% incidence rate in Los Angeles in high-risk Black MSM (Koblin et al., 2012)
  - Infections were <30 y.o., most under age 22

- HPTN 073 showed similar incidence rate in Los Angeles in the presence of oral daily Truvada for high-risk Black MSM (Wheeler et al., 2016)
  - Infections were <22 y.o.

- HIV incidence in methamphetamine using MSM is 6.1% (Reback et al., 2014)
WHAT’S NEXT?

- HIV incidence in key populations in Los Angeles is higher than most other urban areas in U.S. (comparable to Sub-Saharan Africa)

- Daily oral antiretrovirals as Pre-Exposure Prophylaxis (PrEP) have limited impact, especially for those living with chaotic life situations

- Two new and potentially high-impact approaches to PrEP are now (or shortly will be) available in L.A. County

- Linkages to these research opportunities:
  - (866) 449-UCLA (8252) at the UCLA Vine Street Clinic
  - (310) 557-9062 at the UCLA CARE Clinic
Getting to Injectable PrEP: From Truvada to HPTN 083
Clinical Trial Evidence for HIV Prevention Options (February 2016)

Prevention of sexual transmission

- PROUD – daily oral TDF/FTC (MSM – United Kingdom)
- IPERGAY – event-driven TDF/FTC (MSM – Canada, France)
- Partners PrEP – daily oral TDF/FTC (Serodiscordant couples – Kenya, Uganda)
- Partners PrEP – daily oral TDF (Serodiscordant couples – Kenya, Uganda)
- TDF2 – daily TDF/FTC (Heterosexual men and women – Botswana)
- iPrEx – daily oral TDF/FTC (MSM – North and South America, South Africa, Thailand)
- CAPRISA 004 – BAT-24 dosing vaginal tenofovir gel (Women – South Africa)
- RV 144 – six injectable ALVAC/AIDSVAX (Heterosexual men and women – Thailand)
- The Ring Study – monthly vaginal ring containing dapivirine (Women – South Africa, Uganda)
- ASPIRE – monthly vaginal ring containing dapivirine (Women – Malawi, South Africa, Uganda, Zimbabwe)
- MTN 003/VOICE – daily dosing vaginal tenofovir gel (Women – South Africa, Uganda, Zimbabwe)
- FACTS 001 – event-driven vaginal tenofovir gel (Women – South Africa)
- MTN 003/VOICE – daily oral TDF (Women – South Africa, Uganda, Zimbabwe)
- MTN 003/VOICE – daily oral TDF (Women – South Africa, Uganda, Zimbabwe)

Effect size (CI)

- 86% (58; 97)
- 86% (44; 99)
- 75% (55; 87)
- 67% (44; 81)
- 62% (22; 84)
- 44% (15; 63)
- 39% (6; 60)
- 31% (1; 51)
- 27% (1; 46)
- 15% (-21; 40)
- 6% (-21; 40)
- 0% (-40; 30)
- 4% (-49; 27)
- 49% (-129; 3)

Effectiveness (%)

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- 49% (-129; 3)

Adapted from: Salim S. Abdool Karim, CAPRISA
Total Incidence and Growth Trend of FTC/TDF for PrEP


Bush S, et al. ASM/ICAAC 2016; Boston, MA. #2651
FTC/TDF for PrEP Utilization Compared With Population and New HIV Infections


- AA: 0.62
- White: 0.12
- Hispanics: 0.18
- Asians: 0.0237
- Multiracial/Other: 0.03

Total FTC/TDF for PrEP Utilization by Race/Ethnicity, Sept 2015, US

- AA: 74%
- White: 12%
- Hispanics: 10%
- Asians: 4%


- 0.2728

FTC/TDF for PrEP use among AA and Hispanics is low relative to the rate of new HIV infections

a. [https://www.census.gov/quickfacts/table/PST045215/00](https://www.census.gov/quickfacts/table/PST045215/00)
b. These data represent 43.7% (n=21,463) of unique individuals who have started TVD for PrEP from 2012-3Q2015.
c. Other indicates American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander. CDC. *HIV Surveillance Report, 2014*

Bush S, et al. ASM/ICAAC 2016; Boston, MA. #2651
New HIV Diagnoses in 2010-2012 by ZIP Code and Service Planning Area (SPA) in Los Angeles County (N=5,958)
The PrEP Pipeline: Looking past TDF/FTC

- Maraviroc – HPTN 069/ACTG A5305
- TAF – Macaque protection (?) but low tissue levels
- Long Acting Therapies
  - Rilpivirine (TMC278) – HPTN 076
  - Cabotegravir (GSK1265744) – HPTN 077/HPTN 083/ÉCLAIR
  - Immunotherapies – VRC01
  - Implantable devices
- More on Intermittent (i)PrEP
- Special populations
  - HPTN 073 – BMSM
  - ATN 110/113 – Youth
- Combinations of interventions

2. Garrett K, CROI 2016
The PrEP Pipeline: Looking past TDF/FTC

- Maraviroc – HPTN 069/ACTG A5305\(^1\)
- TAF – Macaque protection (?) but low tissue levels\(^2\)
- Long Acting Therapies
  - Rilpivirine (TMC278) – HPTN 076
  - Cabotegravir (GSK1265744) – HPTN 077/HPTN 083/HPTN 084/ÉCLAIR\(^3\)
  - Immunotherapies – VRC01
  - Implantable devices
- More on Intermittent (i)PrEP
- Special populations
  - HPTN 073 – BMSM\(^4\)
  - ATN 110/113 – Youth\(^5,6\)
- Combinations of interventions

2. Garrett K, CROI 2016
A phase 2 safety study designed to answer: Could daily oral maraviroc, a CCR5 receptor antagonist, be a next-gen PrEP agent for men and/or women?
HPTN 069 / ACTG A5305: Participants

• N = 406 individuals enrolled
• 100% male at birth; 7 (2%) transgender
• Median age 30 (range 18, 70)
• 28% black, 22% Latino, 62% white, 10% other (participants could report more than one)
• 20% high school education or less, 67% some college or more, 13% advanced degrees

• 31 (8%) had 34 STIs during study screening:
  – 15 (4%) chlamydia, 5 (1%) gonorrhea, 14 (3%) syphilis
HPTN 069 / A5305: Results

• No differences by study arm in:
  – proportion who discontinued study drugs (p=0.6)
  – time to permanent study drug discontinuation (p=0.6)

• There were 67 grade 3-4 AEs
  – No differences in occurrence or rate among the study arms (p>0.05 in pairwise comparisons)

• 90 (22%) had 115 STI diagnosed during study f/u

• Plasma Drug Concentrations:
  – Random subset across 4 study arms (n=160)
  – All study drugs in regimen detectable in 83% (week 24) and 77% (week 48)
    • No differences between the study arms (p>0.3)
HPTN 069 / A5305: HIV Infections

- 5 new HIV infections during the study
- Annual incidence rate 1.4% [95% CI: 0.8%, 2.3%]

<table>
<thead>
<tr>
<th>#</th>
<th>Demos. (age, race/ethnicity, HIV risk)</th>
<th>Study arm</th>
<th>First reactive HIV+ test (week)</th>
<th>HIV RNA (cps/mL)</th>
<th>CD4 cells (/mm³)</th>
<th>HIV tropism</th>
<th>Genotypic drug resistance</th>
<th>Plasma drug conc. at seroconversion visit (ng/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20, black MSM</td>
<td>MVC+ TDF</td>
<td>4</td>
<td>122,150</td>
<td>357</td>
<td>R5</td>
<td>none</td>
<td>MVC=0† TFV=0</td>
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<tr>
<td>2</td>
<td>61, Asian MSM</td>
<td>MVC alone</td>
<td>16</td>
<td>981</td>
<td>294</td>
<td>R5</td>
<td>none</td>
<td>MVC=145</td>
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<tr>
<td>3</td>
<td>21, mixed MSM</td>
<td>MVC alone</td>
<td>24</td>
<td>106,240</td>
<td>325</td>
<td>R5</td>
<td>none</td>
<td>MVC=0†</td>
</tr>
<tr>
<td>4</td>
<td>35, white MSM</td>
<td>MVC alone</td>
<td>32</td>
<td>13,626</td>
<td>828</td>
<td>R5</td>
<td>none</td>
<td>MVC=6.7</td>
</tr>
<tr>
<td>5</td>
<td>36, black MSM</td>
<td>MVC alone</td>
<td>48</td>
<td>52,191</td>
<td>804</td>
<td>R5</td>
<td>none</td>
<td>MVC=0.7</td>
</tr>
</tbody>
</table>

* expected pre-dose steady state MVC = 32 ng/ml
† undetectable plasma drug concentrations at every study visit
HPTN 076

A phase 2 safety study designed to answer:
Could injectable rilpivirine, a FDA-approved
NNRTI in its oral formulation, be a useful
sustained-release PrEP agent?
Long Acting Rilpivirine (TMC278)  
HPTN 076: Phase 2 Safety

- TMC278 LA is a novel poloxamer 338-containing formulation of TMC278. TMC278 LA is long-acting suspension and well-suited for delivery via IM injection
- HPTN 076 enrolling at 4 sites, low-risk HIV-uninfected women (NY, NJ, Zim, SA)
- Fully enrolled, Data available 2017
**HPTN 076: Safety and acceptability of injectable rilpivirine (TMC278 LA) for PrEP**

136 HIV-uninfected, women ages 18-45 years

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>52</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARM 1</strong>&lt;br&gt;N = 91</td>
<td>Daily oral TMC278</td>
<td>Six injections of TMC278 LA 1200 mg every 8 weeks</td>
<td>Follow-up phase (tail phase)</td>
</tr>
<tr>
<td><strong>ARM 2</strong>&lt;br&gt;N = 45</td>
<td>Daily oral placebo</td>
<td>Six injections of TMC278 LA placebo every 8 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**HPTN**

HIV Prevention Trials Network
HPTN 076 – Study Sites and Status

US Sites
- Bronx, NY
- Newark, NJ

International Sites
- Cape Town, South Africa
- Harare, Zimbabwe

Primary Endpoint- September, 2016
Last Study Visit- February, 2017
CABOTEGRAVIR

The artist formerly known as GSK1265744
Or “744”
**Cabotegravir (GSK 1265744) development**

**Early Phase**
- NHP Models
- First-in-human/Phase 1
- Cardiac Safety, DDI

**Indication**
- Treatment
  - Prevention cis women
  - Prevention MSM/TGW

**Phase 2a**
- LATTE-1
  - HPTN 077*
  - ECLAIR

**Phase 2b ± 3**
- LATTE-2 Pivotal Phase 3
  - HPTN 084
  - HPTN 083

*INCLUDES BOTH MEN AND WOMEN
HPTN 077 – Phase 2a

US Sites
- Los Angeles, California
- San Francisco, California
- Washington, DC
- Chapel Hill, North Carolina

International Sites
- Soweto, South Africa
- Vulindlela, South Africa
- Lilongwe, Malawi
- Rio de Janeiro, Brazil

Fully Enrolled as of May 27, 2016
67% Women

Primary Endpoint- March, 2017
Last Study Visit- January, 2018
HPTN 083
an HIV prevention clinical trial

Coming Soon to UCLA CARE and Vine Street Clinic
HPTN 083: Treatment Arms

Group A
- Cabotegravir (CAB) injection
- Cabotegravir (CAB) pill
- TDF/FTC pill
- Placebo for cabotegravir (CAB) injection
- Placebo for cabotegravir (CAB) pill
- Placebo for TDF/FTC pill

Group B
- Cabotegravir (CAB) injection
- Cabotegravir (CAB) pill
- TDF/FTC pill
- Placebo for cabotegravir (CAB) injection
- Placebo for cabotegravir (CAB) pill
- Placebo for TDF/FTC pill
HPTN 083: A “3 STEP” Study

[Diagram showing the different steps and phases of the study, including screenings, medications, and timelines.]
Protocol Objectives

Primary Objectives
- Efficacy of CAB vs. TDF/FTC
- Safety of CAB vs. TDF/FTC

Secondary Objectives
- Efficacy in pre-specified subgroups of CAB vs. TDF/FTC
- Kidney, liver, and bone safety in CAB vs. TDF/FTC
- ART resistance in seroconverters on CAB vs. TDF/FTC
- HIV incidence based on strata of study product adherence
- Acceptability and preferences for oral vs. injectable PrEP

Tertiary Objectives
- Rates, patterns, correlates of adherence
- Changes in sexual risk behavior (self-report and biomarkers, i.e., STIs)
- Cost effectiveness considerations
Study Population

Cis-MSM and TGW, 18 yo or older, at high-risk for HIV acquisition defined as:

- In past 6 months: Any ncRAI; >5 partners; stimulant drug use; rectal or urethral STI
- Or
- SexPRO risk score ≤16

Enrollment goals:
- Minimum 50% of US enrollment BMSM (~ 950)
- Overall minimum 10% TGW (~ 450)
- Overall > 50% under age 30
HPTN 083 Sites

**South Africa**
- Groote Schuur HIV CRS

**Asia (Thailand and Vietnam)**
- CMU HIV Prevention CRS
- Silom Community Clinic CRS
- Thai Red Cross (TRC-ARC) CRS
- Yen Hoa Health Clinic CRS

**Latin America (Argentina, Brazil, Peru)**
- Fundación Huésped CRS
- Hospital General de Agudos JM Ramos Mejía CRS
- Instituto de Pesquisa Clínica Evandro Chagas (IPEC) CRS
- Hospital Nossa Senhora da Conceição CRS
- University of Sao Paulo CRS
- Centro de Referencia e Treinamento DST/AIDS CRS
- Asociacion Civil Selva Amazonica (ACSA) CRS
- Barranco CRS
- San Miguel CRS
- CITBM CRS
- Via Libre CRS

**United States**
- Alabama CRS
- Adolescent and Young Adult Research at the CORE Center (AYAR at CORE) CRS
- Bridge HIV CRS/ East Bay AIDS Center (EBAC) CRS
- Bronx Prevention Research Center CRS
- Chapel Hill CRS
- Children’s Hospital Colorado CRS
- Cincinnati CRS
- Fenway Health (FH) CRS
- George Washington University CRS
- Greensboro CRS
- Harlem Prevention Center CRS
- Hope Clinic of the Emory Vaccine Center CRS
- Houston AIDS Research Team (HART) CRS
- Johns Hopkins University CRS
- New Jersey Medical School CRS
- New Orleans Adolescent Trials Unit CRS
- New York Blood Center CRS
- Ohio State University CRS
- Penn Prevention CRS
- Ponce de Leon Center CRS
- St. Jude Children’s Research Hospital CRS
- UCLA CARE Center CRS
- UCLA Vine Street Clinic CRS
- UIC Project WISH CRS
- University of Miami AIDS Clinical Research Unit (ACRU) CRS
- Washington University Therapeutics (WT) CRS
- Weill Cornell Chelsea CRS
HPTN 083 Sites – Phase 3
43 Sites in 8 Countries

Anticipated Start – 3rd Q 2016 US Sites
Non-US TBD*
*Based on local regulatory approvals
HPTN 083

• UCLA CARE Center
  – Michelle Simek
    msimek@mednet.ucla.edu
    (310) 557-2044

• UCLA Vine Street Clinic
  – Chris Blades
    cblades@mednet.ucla.edu
    (323) 461-3106, ext 29
    (866) 449-UCLA
Slides adapted from Shelly Karuna/HVTN and Phil Andrew/HPTN
Where is the HIV Prevention field?
The Context for The AMP Study

▪ Despite many advances in prevention and treatment, the global HIV epidemic continues.

▪ Millions of new HIV infections occur every year.

▪ The current prevention toolbox is insufficient to curb the epidemic.

▪ We cannot treat our way out of the epidemic.
HIV in the US: the epidemic goes on

**Figure 1. HIV Incidence.** Estimated New HIV Infections in US Subpopulations, 2010; Source: CDC

**Figure 2. HIV Prevalence.** Overall sample refers to the general US adult population. Survey total and remaining circles refer to transgender respondents to the National Transgender Discrimination Survey. Source: NTDS
What do we have to address the epidemic?

- Education and behavior modification
- Condoms, and other barrier methods
- Treatment/prevention of drug/alcohol abuse
- Clean syringes, i.e. needle exchange programs
- Interruption of mother-to-child transmission
- Circumcision for female-to-male transmission
- HIV/STI Testing
- Antiretroviral treatment as prevention
- Post-exposure prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)*
- Topical microbicides†
- Vaccination‡

*Daily Truvada®; alternate regimens still in research
†Still in research
‡Still in research

With thanks to Carl Dieffenbach & Jeff Schouten
So let’s look at an option to fill a gap: AMP

- AMP stands for Antibody Mediated Prevention

- This is the idea of using an antibody made in the lab and giving it to people directly, i.e. using an intravenous (IV) infusion, to prevent HIV infections
Who is doing The AMP study?

The study is being conducted by two groups, the HIV Vaccine Trials Network and the HIV Prevention Trials Network.

Another name for The AMP Study is HVTN 704/HPTN 085
AMP Study Research Sites
HVTN 704/HPTN 085 US Sites

- Altanta, GA (2 clinic locations)
- Birmingham, AL
- Boston, MA (2 clinic locations)
- Chapel Hill, NC
- Cleveland, OH
- Los Angeles, CA
- Nashville, TN

- Newark, NJ
- New York City, NY (4 clinic locations)
- Philadelphia, PA
- Rochester, NY
- San Francisco, CA
- Seattle, WA
- Washington, DC
The AMP Study (HVTN 704/HPTN 085): Defining a new path forward

This is the first trial to assess if antibodies can be used to prevent HIV infection, similar to how antibodies are used to prevent other infectious diseases.
How Does an Antibody Work?

**NEUTRALIZATION**
Binds to HIV & blocks its attachment to host cells

**OPSONIZATION**
(“buttering the toast”)
Binds to HIV, then binds to a macrophage; the macrophage then eats the HIV

**SENSITIZATION**
(“the lookout for the hitman”)
Binds to HIV, then binds to an NK cell; the NK cell then spills its “poison” to kill HIV
Neutralizing Antibodies

Thanks to Lisa Donohue for these images.
Meet VRC01: The AMP Study antibody

This antibody is called **VRC01**. It was discovered by scientists at the US National Institutes of Health.

In lab studies, it has been able to block HIV in about 90% of the different types of HIV that it has been tested against.

Gray: gp120
Red: CD4 binding site (CD4bs)
Purple & Green: VRC01 attached to the CD4bs

Photo: NIAID/NIH Vaccine Research Center (VRC)
VRC01 attaches to the CD4 binding site on gp120

The GP 120 Protein

Red lines = linear epitopes
Red circle = the CD4 binding site

Image credit: NIAID
VRC01 in Preclinical (NHP) Trials

20 mg/kg infusion of VRC01

RECTAL CHALLENGE
4/4 PROTECTED

VAGINAL CHALLENGE
4/4 PROTECTED

0/4 protected

VRC01 in Preclinical (NHP) Trials

VRC01
Control

1/4 protected

VRC01
Control
VRC01 in Phase 1 Human Trials: Safe & Well-Tolerated

- 3 Phase 1 trials: VRC601, VRC602, HVTN 104

- Safe, well-tolerated in >100 participants
  - No related serious “adverse events”
  - Mild adverse events only, which included mild lab changes in liver & kidney tests
The Main AMP Study Questions

- Is the VRC01 antibody safe to give to people?
- Are people able to “tolerate” the antibody without becoming too uncomfortable?
- Does the antibody lower people’s chances of getting infected with HIV?
- If the antibody does lower people’s chances of getting infected with HIV, how much of it is needed to provide protection from HIV?
PrEP in The AMP Study

• PrEP offered to participants as part of risk reduction counseling
• Referral to PrEP providers (not provided as part of study protocol)
• Truvada provided at no drug cost for interested ppts for length of enrollment
AMP in a Post-PrEP World: What’s the Point?

• If participants will have free access to PrEP, will you be able to see an effect of VRC01?
  • Maybe not
    • Truvada is known to be effective in preventing HIV-1
    • But many people have trouble taking Truvada every day
  • Other questions are more interesting (right now)
    • Antibody-mediated prevention could open up an entirely new pathway for HIV prevention
    • At this time, understanding of how immunologic parameters are affected by a bnMAb and how these can be harnessed as future prevention technologies is more important to this pathway than a simple test of effectiveness
## Study Schema for The AMP Study

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1500</td>
<td>4200</td>
</tr>
</tbody>
</table>

- **10 infusions total**
- **Infusions every 8 weeks**
- **Study duration: ~22 months**
The AMP Study: Selected Eligibility Criteria

- 18-50 years of age
- HIV uninfected
- Risk behavior related criteria:
  - In the Americas: Male or TG who has had condomless anal intercourse with ≥ 1 male or TG partner(s) or any anal intercourse with ≥ 2 male or TG partners in the past 6 months
  - All volunteers in a monogamous relationship with an HIV(-) partner for > 1 year are excluded.
- Volunteers with clinically significant medical conditions are excluded
What will an AMP participant need to do?

- **IV**: receive an IV over a 30-60 minute period every 8 weeks (10 times total)
- **Blood draw**: get a blood draw at the clinic every 4 weeks (includes an HIV test)
- **STI testing**: get STI testing (urine & rectal swabs) about every 6 months
- **Questionnaires**: complete questionnaires about sexual behavior & general health every 4-8 weeks

**STUDY DURATION**: about 22 months
Presenters’ Contact Information

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